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TOWNSEND AND TOWNSEND AND CREW LLP
TWO EMBARCADERO CENTER
8TH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
SCHNIZER, HOLLY G	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 01/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/424,498	SCHWARZ ET AL.	
	Examiner	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,32,35-37,39-41,43-69 and 72-78* is/are pending in the application.

4a) Of the above claim(s) *45-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *31,32,35-37,39,40,43,44,64-69 and 72-78* is/are rejected.

7)☐ Claim(s) *41* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 February 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

The Amendment filed October 6, 2003 has been entered. Claims 70 and 71 have been cancelled and Claims 74-78 have been entered. Therefore, Claims 31-32, 35-37, 39-41, 43-69, and 72-78 are pending, Claims 45-63 are withdrawn as being drawn to non-elected subject matter, and Claims 31, 32, 35, 36, 37, 39, 40, 41, 43, 44, 64, 65, 66, 67, 68, 69, 72-78 have been considered on the merits in this Office Action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-32, 35-37, 39-40, 43-44, 66-69 and new Claims 72 and 73 are rejected under 35 U.S.C. 102(b) as being anticipated by Burnouf-Radosevich et al. (U.S. Patent No. 5,408,039, 1995). It is noted that the references of Turecek et al., Ruggeri et al., and Wise et al. are used as evidence for inherent properties of the preparation of Burnouf-Radosevich et al. in response to Applicants arguments. However, the Burnouf-Radosevich et al. reference alone meets all of the limitations of the claims.

A response to Applicant's arguments is provided after the following review of the Burnouf-Radosevich et al. teachings as stated in the previous Office Action.

Rejection: Burnouf-Radosevich et al. teach that pharmaceutical compositions comprising vWF from vWF-enriched plasma derivatives are very well known in the art (Col. 1-Col. 2). Burnouf-Radosevich et al. disclose a highly purified vWF concentrate that is subjected to a solvent-detergent treatment known for its efficiency in destroying lipid-enveloped viruses (Col. 5, Example and "Viral Inactivation Treatment"). The vWF is synthesized as a pre-pro-peptide. Upon cleavage of the signal peptide, the pro-vWF (containing the propeptide and mature peptide segments) dimerizes, assembles into multimers, and then the propolypeptide (741 aa segment) is removed by proteolytic cleavage. However, cleavage is not always complete. Therefore, it appears that a vWF plasma derivative, such as disclosed in Burnouf-Radosevich et al. would comprise the vWF pro polypeptide, the pro-vWF, as well as the mature vWF. In addition, Burnouf-Radosevich et al. teach that the composition disclosed therein may also comprise Factor VIII (Col. 5, lines 55-60). Therefore, the claims appear to be anticipated by Burnouf-Radosevich et al.

Claim 67 (composition comprising the pro-vWF) is also rejected for the same reasons applied above. Claim 68 is rejected because the fact that pro-vWF is recombinant does not patentably distinguish the composition over that of the prior art since both recombinant and isolated forms of pro-vWF would have the same sequence, structure, and function. Claim 69 is rejected for the reasons stated above. It is known that the propeptide (741 aa segment) is required for factor VIII binding either as part of the pro-vWF or in trans as the propeptide. Thus, since Burnouf-Radosevich et al. teach that the composition may also comprise Factor VIII (Col. 5, lines 55-60) and since this

composition maintains Factor VIII and vWF activity (see Col. 5, lines 64-66), it would be inherent that the pro-vWF complexed to the factor VIII.

Claims 72 and 73 add the limitation that the compositions are formulated for parenteral administration. Such limitation amounts to intended use and the preparations of Claims 72 and 73 do not appear to contain any components not taught in the Burnouf-Radosevich et al. and thus do not patentably distinguish the claimed composition over the prior art.

Response to Arguments:

Applicants argue that the limitation "pharmaceutically effective amount" makes the claimed product patentable over that of the prior art. This argument has been considered but is not deemed persuasive because neither the claims nor the Specification indicate what amounts are considered "pharmaceutically effective" and the claims and Specification do not indicate what pharmaceutical effect the amount is supposed to have. The Specification appears to indicate that an "effective amount" is that amount necessary to obtain a pp-vWF level of at least twice the physiologic amount in human plasma. However, the Specification does not provide any examples of in vivo administration of pp-vWF and does not provide a quantitative value for the amount of pp-vWF necessary to obtain twice the physiological amount in human plasma. Thus, due to this lack of definition for "pharmaceutically effective amount" and absent evidence that trace amounts do not have pharmaceutical effects, this limitation has been treated to encompass a very broad range of pp-vWF concentrations. Absent

evidence that the concentration of pp-vWF in the Burnouf-Radosivich preparation is not "pharmaceutically effective", this argument is not deemed persuasive.

Absent evidence to the contrary, pp-vWF would be present in the Burnouf-Radosivich preparation:

Applicants contend that the examiner has not clearly established that the Burnouf-Radosivich composition *necessarily* contains pp-vWF. To support their argument, Applicants indicate that the vWF propolypeptide concentration is only one tenth of the concentration of vWF in plasma, that the half life of the vWF propolypeptide is less than vWF, and that the isoelectric points of the vWF propolypeptide and vWF differ enough to separate them using anion exchange chromatography. This argument has been considered but is not deemed persuasive because the references cited by the examiner in the previous Office Action (and discussed below) indicate that the vWF propolypeptide is contained in vWF preparations even when the vWF is highly purified and Applicant has not provided any evidence that the Burnouf-Radosivich preparation is free of the vWF-propolypeptide. The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562

F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

The Burnouf-Radosevich et al. procedure for purifying vWF does not contain a step that would separate the propolypeptide from the mature vWF. Burnouf-Radosevich et al. only uses anion exchange chromatography in the purification process. While Applicant indicates that the isoelectric points of vWF and the vWF propolypeptide differ enough to separate by anion exchange chromatography, Applicants did not provide evidence that the purification procedure practiced in the Burnouf-Radosevich reference would have separated all of the vWF propolypeptide to provide a vWF preparation free from the vWF propolypeptide. There are no reports of purifying the propeptide using anion exchange. Rather, the well-known purification procedures for the vWF propolypeptide are by size exclusion or affinity chromatography to ensure that the vWF propolypeptide is separated from the mature vWF. Takagi et al. emphasizes that the propolypeptide was purified by three different affinity chromatographies (see p. 6018, Col. 1, first paragraph). In addition, Borchiellini et al. (Blood (1996): 88(8): 2951-2958; cited in IDS) teach that the propolypeptide composition describe therein was passed through a column containing a monoclonal antibody specific for the mature vWF in order to remove the pro-vWF and mature vWF from the propolypeptide (p. 2952, Col. 2, 2nd paragraph). Finally, even in instances wherein immuno-affinity chromatography (using antibodies specific for the mature vWF) is used to try to separate the propolypeptide from pro-vWF/mature vWF solutions, minute amounts of the propolypeptide are still present in the purified mature vWF compositions (see Turecek et

al. Blood (1999) 94(5): 1637-1647, especially p. 1638, Col. 1, 2nd para. from bottom; previously cited in Paper No. 16). These reference show that purification schemes that even contain steps to eliminate the propolypeptide, fail to eliminate all of the propolypeptide. The Burnouf-Radosevich reference does not contain any steps to eliminate the propolypeptide from the final preparation. Thus, absent any evidence that the Burnouf-Radosevich et al. method involves a step to specifically eliminate the propeptide from the composition isolated therein, it appears that the Burnouf-Radosevich et al. preparation contains at least small amounts of the vWF propeptide.

Absent evidence to the contrary, Pro-vWF would be present in the Burnouf-Radosevich et al. preparation

With respect to pro-vWF, Applicants again argue that it would be rapidly degraded. This argument has been considered but is not deemed persuasive because Applicants have not addressed the evidence that pro-vWF is present circulating in vivo. As stated in the previous Office Action, Wise et al. indicate that pro-vWF cleavage is not required for secretion or multimer formation. Wise et al. state that multimers can be assembled from uncleaved pro-vWF and that uncleaved pro-vWF are present in multimers from endothelial cell culture medium and circulating in vivo (p. 231, section bridging Col. 1 and 2). Ruggeri et al. (Thromb. Haem. (1992) 67(6) 594-599) also state that a certain proportion of normal plasma vWF multimers contain pro-vWF peptide that are secreted from endothelial cells by the constitutive pathway (see p. 594, Col. 2, lines 16-20). It is also noted that Wise et al. show that the pro-vWF is readily apparent in the cell culture medium of cells expressing a wild-type pre-pro-vWF (see Fig. 6A). Applicants, on the

one hand, argue that this evidence that pro-vWF circulates in vivo is not at issue (p. 12, line 3 of part B), and on the other hand, argue that pro-vWF is quickly metabolized in the circulation (bottom of p. 13). Again, however, Applicants have not addressed the evidence that pro-vWF is present circulating in vivo. Moreover, using the references above, the examiner has established that pro-vWF would have been contained in the starting material used in the method of purification by Burnouf-Radosivich. The purification method of Burnouf-Radosivich does not contain a step to remove the pro-vWF and Burnouf-Radosivich does not indicate that the disclosed preparation is free of pro-vWF. The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

****Examiner's note: The following rejection has been reinstated after reconsideration of the Takagi et al. reference and the previous prosecution. In the previous office action the rejection of the claims under 35 U.S.C. 102 over Takagi et al. was withdrawn because Applicants argued that the Coomassie brilliant blue staining of

the purified pp-vWF was not sensitive enough to show contaminating viral proteins. However, this argument does not provide evidence that the Takagi et al. preparation contains contaminating active viral proteins but only that it is not the proper method for determining whether or not it does.

Consequently, this Office Action has not been made final due to the new issues raised.

Claims 31-32, 39-40, 43-44, 64-65, 72, and 74-76 are rejected under 35 U.S.C. 102(b) as being anticipated by Takagi et al. (Takagi et al. (J. Biol. Chem. (1989) 264(11): 6017-1020; ref. AY of IDS of Paper No. 6).

Takagi et al. disclose a composition comprising vWF propolypeptide isolated from human platelets (see p, 6017, Experimental Procedures). Since the vWF propolypeptide is a glycoprotein isolated from platelets it is considered a platelet glycoprotein component (clms 39-40). The purified vWF propolypeptide of Takagi et al. appears to be 95% pure (see SDS-PAGE gel in Fig. 1). The concentration of the vWF propolypeptide preparations disclosed in Takagi et al. were greater than 50 nM (see Fig. 4).

The present claims are drawn to a product-by-process. As evidenced by the prior art, it appears that the vWF propolypeptide was very well known in the art at the time of the invention. While the vWF propolypeptide composition of the prior art appears to have been made by a process different than that claimed, the vWF propolypeptide known in the art is identical in structure and function to the presently claimed polypeptide and would inherently have the same properties and utilities as the

polypeptide presently claimed. Applicants are reminded that something which is old does not become patentable upon the discovery of a new use. The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977) (see MPEP 2112).

In the previous Office Action, the rejection of the claims under 35 U.S.C. 103 was withdrawn because Applicants argued that the Coomassie brilliant blue staining of the purified pp-vWF was not sensitive enough to show contaminating viral proteins. However, this argument does not provide evidence that the Takagi et al. preparation contains contaminating viral proteins but only that it is not the proper method for determining whether or not it does. As explained in the previous rejection, the office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989). In the present case, there is no evidence and no reason to believe that the Takagi et al. purified preparation of pp-vWF contains contaminated active viruses. Thus, absent evidence to the contrary, the rejection of the claims as being anticipated over Takagi et al. is reinstated as discussed below.

In the present case, it appears that the claimed compositions are patentably indistinguishable from the prior art, absent evidence to the contrary. In the alternative, the claimed compositions would be obvious over the prior art as described below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31, 32, 39, 40, 43, 44, 64, 65, 72, and new Claims 74-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takagi et al. (J. Biol. Chem. (1989) 264(11): 6017-6020) in view of EP 0 131 740 (cited in IDS of Paper No. 20), Blann et al. (Eur. J. Vasc. Surg. (1994) 8 : 10-15; cited in IDS) and Applicants admissions in the instant Specification.

The response to Applicants arguments follows a restatement of the rejection below. The rejection below also addresses new issues raised in the new claims 74-76.

Rejection:

Takagi et al. disclose a composition comprising vWF propolypeptide isolated from human platelets (see p, 6017, Experimental Procedures). The purification process of Takagi et al. includes three affinity chromatography steps and the resulting propeptide appears to be at least 95% pure. Takagi et al. indicate that concentrations as low as 2 µg/ml of the vWF propolypeptide were sufficient to inhibit collegen-induced platelet aggregation (p. 6019, Col. 2). Takagi et al. disclose using as much as 5.5 µg/ml vWF propolypeptide (see Fig. 4). Based on the molecular weight of vWF propolypeptide as reported by Takagi et al. as being 100,000 (p. 6018, Col. 1, Fig. 1), the reported concentrations are considered to be 20 nM and 55 nM, respectively. Since the vWF propolypeptide is a glycoprotein isolated from platelets it is considered a platelet glycoprotein component (clms 39-40). Takagi et al. concludes that pp-vWF has a strong affinity to collagen and that it inhibits collagen-induced aggregation of human platelets and suggests that pp-vWF and vWF may have opposing effects on hemostasis (see abstract). Takagi further concludes that pp-vWF could have a unique function in hemostasis independent of mature vWF, since it is known to be released from platelets upon activation by thrombin, collagen, and ADP. It is stated that since pp-vWF inactivates collagen upon short incubation, released pp-vWF should immediately bind to exposed collagen layer at the site of vessel wall injury and may prevent further adhesion

of platelets to subendothelium (seep. 6018, Col. 2, lines 2-10 from bottom). The Takagi et al. preparation contains at least 50 nM pp-vWF (Fig. 4, figure legend).

Takagi et al. do not teach that the purified vWF propolypeptide has been treated for at least one of virus inactivation or virus removal or that the pp-vWF composition is appropriate for therapeutic administration.

EP 0 131 740 teaches a method for making a composition containing blood proteins free of lipid containing viruses.

The purification of pp-vWF is known in the art as evidenced by Takagi et al. as well as admitted by the Specification (p. 4. last paragraph). A wide variety of methods of treating compositions for virus removal or inactivation are very well known in the art (see Specification, p. 7, first paragraph; or EP 0 131 740, cited in IDS of Paper No. 20).Therefore, making a composition identical to that of the present invention was well within the skill of the art at the time of the invention and one only needs motivation to treat the composition of Takagi et al. for viral removal or inactivation. This motivation is found in the combined teachings of Takagi et al. and Blann et al.

Blann et al. teaches (as noted by the Specification as originally filed, p. 3, paragraph 3) that vWF levels are increased with risk factors for atherosclerosis and in patients with diffuse arterial disease (p. 13, Col. 2, lines 1-3). Blann et al. also suggests that future therapeutic strategies could involve agents that oppose vWF (p. 13, Col. 2, last paragraph). One disadvantage associated with coagulation promoting preparations is the risk of arterial thrombosis. Takagi et al. suggests that pp-vWF inhibits the collagen-induced platelet aggregation and has an opposite effect on platelet

adhesion. Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention, to purify the propeptide by modifying the method of Takagi et al. to include a step of virus removal or inactivation as taught in EP 0 131 740. One of ordinary skill would have had a reasonable expectation of success in using such a composition since Takagi et al. teaches that the propeptide activity opposes that of the mature vWF and Blann et al. describe a need in the art for preparations that would oppose the high vWF levels and activity that are associated with atherosclerosis and arterial disease. Thus, the claims are unpatentable over the prior art.

Response to Arguments:

As admitted in the Specification (p. 4, last paragraph), the purification of pp-vWF and virus removal or inactivation (p. 7, first paragraph) were very well known processes at the time of the invention. Therefore, the present issue at hand is whether or not one of ordinary skill in the art at the time of the invention would have been motivated to combine these well-known methods to make the claimed product.

Applicants argue that there is no motivation to combine the cited references because there is no evidence that would enable one to conclude that high vWF levels were a potential cause of arterial disease and because Blann et al. indicates that further investigation was needed to understand the association between high vWF levels and diseases such as atherosclerosis. Applicants argue further that the Takagi et al. results were in vitro and may not apply in vivo. Overall, Applicants contend that the motivation presented in the previous Office Action is at best an "obviousness to try rationale"

because Blann et al. and Takagi et al. only provide an invitation to determine whether or not pp-vWF has collagen inhibitory activity in vivo.

These arguments have been considered but are not deemed persuasive for the following reasons:

Contrary to Applicants assertions, Blann et al. does provide suggestion that vWF is a causal factor in various types of atherosclerosis. First, Blann et al. emphasizes that vWF levels are raised in patients with atherosclerosis or related diseases (see paragraph bridging p. 12-13). Secondly, Blann et al. repeatedly suggests that high levels of vWF might predispose to or promote atherosclerosis (p. 13, 1st Col. Middle and last paragraph) and that reducing vWF levels might be a future therapeutic approach (p. 13, last paragraph). Applicants imply that Blann et al. concludes that there is no data in humans that would allow conclusion that low vWF levels protect from atherosclerosis. However, when the citation is read in its entirety and with the knowledge of the teachings of Takagi et al., this statement does not imply that Blann et al. concludes that vWF is not a causative factor. Blann et al. merely states that due to the complexity of von Willebrand disease and due to the added complexity of its treatment with vWF and factors that induce vWF release, von Willebrand disease cannot be used as a model for low vWF. Moreover, Takagi et al. teaches that pp-vWF is also low in patients with von Willebrand disease (p. 6017, Col. 2, first paragraph). Thus, one of ordinary skill in the art, with Blann et al. and Takagi et al. in hand, would not conclude that vWF is not a causative factor in atherosclerosis and related diseases.

Thrombus formation is a key event in the origin and progression of atherosclerosis (Blann et al. p. 10, first line). Mature vWF promotes collagen-platelet interaction and subsequently thrombus formation (see Takagi et al. p. 6018, Col. 2, 2nd paragraph) and is found at highest concentrations in severe atherosclerosis (Blann et al. (p. 12, Col. 1, 2nd paragraph). Takagi et al. found that pp-vWF effectively causes collagen to lose its platelet aggregation activity (Takagi et al. (Col. 2, beginning at line 10, 2nd paragraph). Thus, one of ordinary skill in the art would have had a reasonable expectation of success in using pp-vWF to counteract the platelet aggregation activities of vWF using pp-vWF since Takagi et al. provides evidence that pp-vWF has that activity. (The examiner has considered Applicants argument that the in vitro results of Takagi et al. may not be representative of what occurs in vivo, however, does not deem it to be persuasive because Applicant has not provided any evidence that the in vitro results of Takagi et al. would not represent the activity of pp-vWF in vivo. Moreover, the examiner notes that the present Specification does not include any in vivo activities of the pp-vWF and only shows results of in vitro studies.) Blann et al. suggests that agents that lower vWF concentration might be useful in the treatment of atherosclerosis and related diseases and Takagi et al. teaches that pp-vWF counteracts mature vWF. The suggestion of Blann et al. and the knowledge of the teachings of Takagi et al., at the very least, would have motivated one of ordinary skill in the art to characterize the in vivo activities of pp-vWF as a potential therapeutic agent. Pursuing such research and trials, one of ordinary skill in the art would have wanted to obtain the most highly purified preparations of pp-vWF and would have included steps of eliminating any viral proteins

that would contaminate the preparation and potentially cause erroneous results. In other words, in testing a potential therapeutic agent, one of ordinary skill in the art would have wanted to use a preparation that was representative of that that would be used in therapy. One of ordinary skill in the art at the time of the invention would have had a reasonable expectation of obtaining highly pure preparations of pp-vWF since purification methods for pp-vWF were well known (as evidenced by Takagi et al.) and since virus removal methods were well known (as evidenced by EP 0 131 740). Therefore, in the present case, the combined references provide 1) methodology to make the claimed product (see Takagi et al. and EP 0 131 740), 2) a suggestion to use the claimed product as a pharmaceutical (see Takagi and Blann et al.), and 3) evidence suggesting such use would be successful (see Takagi et al. and Blann et al.). The rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 77 and 78 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. A pharmaceutical preparation for treating blood coagulation disorders wherein the preparation comprises at least 10 nM or at least 100 nM pro-vWF is not enabled by the disclosure.

The instant specification does not specifically provide a method of purification of pro-vWF but only refers to Fischer et al. (FEBS Letters 351, 345-348 (1994)) or Borchiellini et al. (Blood 88(8) 1996, 2951-2958) for instruction as to how to purify pro-vWF and the propeptide. However, while Fischer et al. and Borchiellini et al. teach the expression of pro-vWF and not its purification. A search of the prior art did not reveal a protocol for the purification of pro-vWF specifically. The closest reference found to obtaining such a composition was Turecek et al. (Blood (1999) 94(5): 1637-1647) and Varadi et al. (Thromb. Haemost. (2001) 86: 1449-1458; cited in IDS of Paper No. 20) which were published after the filing date of the present application. Turecek et al. teach purification of the pro-vWF by immuno-affinity chromatography using an antibody to the mature vWF (p. 1638, second paragraph from bottom) resulting in a composition comprising pro-vWF that was 50% pure at best (see p. 1640, Col. 1, Results). Likewise, the pro-vWF described in Varadi et al. is less than 50% pure (they report equal amounts of mature and pro-vWF and less than 2% pp-vWF; see para. bridging p. 1449-1450). The Specification and prior art also did not teach any method of virus removal or inactivation that would preserve the concentration of pro-vWF at least 10 or at least 50 nM. Since Applicants state that the pro-vWF is highly labile (see Paper No. 19, p. 5) and since there is no evidence of art prior to the invention that teaches the purification of pro-vWF, such a teaching would have been required in order for one of skill in the art to make the pro-vWF pharmaceutical compositions having the claimed concentrations.

Claim Objections

Claim 41 is objected to for depending from a rejected claim but would be allowable if rewritten in independent form including all of the limitations of the claim from which it depends.

Conclusions

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
January 6, 2004

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER